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The Auditory, Vestibular, and Oculomotor System in Facioscapulohumeral Dystrophy

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Verhagen WIM, Huygen PLM, Padberg GW. The auditory, vestibular, and oculomotor system in facioscapulohumeral dystrophy. Acta Otolaryngol (Stockh) 1995; Suppl 520: 140–142.

Auditory, vestibular and oculomotor function tests were performed in 14 FSHD patients (7 men, 7 women, aged 19–74 years) with autosomal dominant facioscapulohumeral dystrophy (FSHD) due to chromosome 4q35 associated DNA rearrangements. (Cochlear) sensorineural hearing loss (SNHL) in excess of that expected for their age was found in 6 patients: in 3 at the higher frequencies and in 3 also at the lower (speech) frequencies. Brain-stem auditory evoked potentials were generally normal. Oculomotor functions were normal. Four patients showed vestibular hyperreflexia, perhaps secondary to diminished head movements. Despite the apparent genetic homogeneity of the present patients, the above-mentioned findings showed significant associations with certain families, the cases of new mutations, or a certain generation. Therefore, FSHD in our patients demonstrated clinical heterogeneity. *Key words:* hearing loss, brain-stem auditory evoked potentials, vestibulo-ocular reflex gain, genetics.

INTRODUCTION

Facioscapulohumeral (muscular) dystrophy (FSHD) is a progressive autosomal dominant disorder with almost complete penetrance and variable expression (1–3). The FSHD gene has been mapped to chromosome 4 (4). Associated findings are hearing loss (5–11) or hearing loss, Coats' disease and mental retardation in various combinations (12–18). Sensorineural hearing loss (SNHL) may be associated with vestibular and oculomotor impairment in neuromuscular disease (19); we therefore investigated the auditory, vestibular and oculomotor systems in FSHD patients.

MATERIAL AND METHODS

Auditory, vestibular and oculomotor function tests were performed on 14 patients (7 men, 7 women, age range 19–74 years) with autosomal dominant FSHD, all of whom showed linkage to the markers D4S171 and D4S139 which are located in the region 4q35-qter (4, 20), or DNA rearrangements with p13E-11 (21, 22). Five families (12 patients) with more than one affected subject in more than one generation were involved. Two patients represented new mutations. The clinical diagnosis was confirmed by performing extensive diagnostic procedures including electromyography and muscle biopsy on at least one affected person in each family.

Auditory system

Pure-tone audiograms (allowing for presbycusis) and brain-stem auditory evoked potentials (BAEPs) were obtained and analysed as previously reported (19). Interwave delay (IWD) relates to a significant

increase in the latency difference between waves of the I–V complex. Significant IWD was detected by comparing the latency differences (mean of rarefaction and condensation) to the 95% sex-related confidence limits pertaining to the corresponding intensity level which had been established with this equipment at our laboratory.

Vestibular system

Eye movements were recorded with direct-current electro-oculography (EOG). Vestibular tests were conducted with the patient in the dark with his/her eyes open. Velocity step (VS) tests (90°/s) were performed with a rotatory chain (Tönnies). The following response variables were used to characterize the vestibulo-ocular reflex (VOR): initial velocity (V, 90% confidence limits 30 to 65°/s), time constant (T, 11 to 26 s) and "Gesamtamplitude" or cumulative eye displacement ($G = VT$, 485 to 1135°) (23). In the caloric test, the response variable was the maximum slow phase velocity of nystagmus at the culmination of the response with 95% confidence limits at 7°/s and 45°/s. For the side effect it was arbitrarily assumed that a relative side difference—(difference/sum)·100%—in excess of 20% indicated unilateral hypofunction (24).

Oculomotor system

Gaze positions, saccades, smooth pursuit and optokinetic nystagmus responses were elicited and analyzed as previously reported (19).

Statistical tests

For each test, individual values were compared to the above-mentioned limiting values. Differences in the

relative frequencies of any feature were tested in a 2×2 contingency table using Fisher's exact probability test. Only significant findings ($p < 0.05$) are mentioned below. For the finding of any specific feature in a given relative frequency, the appropriate binomial distribution was calculated for the given sample size and the chance of occurrence (derived from the corresponding confidence limit) to test whether this feature occurred more often than could be explained by false positivity.

RESULTS

Auditory system

Pure-tone audiograms. Pure-tone hearing thresholds were normal for the patient's age (i.e., $< P95$ presbycusis) at all the frequencies in 8 patients bilaterally. The finding that 7 out of the 8 members of two families had normal hearing, while only 1 out of the 6 other patients had normal hearing was significant. Another significant finding was high-tone SNHL in 3 patients, which was significantly associated with new mutations (2 patients). High-tone SNHL was a significant finding in the young patients: 3 out of the 4 patients aged 19–41 years showed this feature, while it did not occur in any of the 10 patients aged 46 years and older. Significant low-tone SNHL was also found in a significantly high number of cases ($n = 3$); 2 patients were sibs, which was a significant finding. All 6 patients with significant SNHL had normal BAEP findings, except for one patient; their hearing loss was therefore attributed to cochlear involvement. A significant finding in the 2 oldest patients was an air-bone gap caused by occlusion of the external auditory meatus by an extremely flaccid skin.

Brain-stem auditory evoked potentials. BAEP findings were normal in most of the patients. Two patients showed a significant I-V IWD (0.41–0.53 ms), which was a bilateral finding in 1, and a (unilateral) III-V IWD (0.27–0.37 ms) was found in 2 patients.

Vestibular system. None of the patients showed any spontaneous nystagmus (eyes open in the dark). Two patients showed a significant side effect in their caloric responses (64% and 32%, respectively). Normal VS responses were found in 7 patients. Three patients showed hyporeflexia. Four of the women (significant) showed vestibular hyperreflexia (VH). When only the women ($n = 7$) were taken into account there was a significant family association: the women ($n = 3$) with a high VOR gain belonged to two families. All 3 women with a high VOR gain had FSHD in the 5th generation, whereas the other 4 women with a normal VOR had FSHD as a new mutation or in the 2nd or 3rd generation. The signifi-

cant finding (high VOR gain in women from certain families) can therefore also be said to be associated with generation 5.

Oculomotor system

None of the patients showed any gaze-evoked nystagmus or limitation of eye movements; saccades, smooth pursuit and optokinetic nystagmus responses were normal in all of the patients.

DISCUSSION

We found a considerable variability in SNHL in our FSHD patients. High-tone SNHL ($n = 3$) and low-tone SNHL ($n = 3$) were significant findings and there were significant associations with certain families, the cases with new mutations, and young age. The general lack of any hearing loss in some families and the occlusion of the external auditory meatus in the 2 oldest patients were also significant findings. Brouwer et al. (11) also concluded that there were incomplete penetrance and variable expression of high-tone SNHL. Involvement of the higher frequencies has been reported repeatedly (5, 6, 8, 10–12, 16, 18). Most of the FSHD patients in the literature who were found to show hearing loss ($n = 38$) were younger than our 6 patients with SNHL.

Voit et al. (10) suggested that in FSHD, SNHL initially involves high-frequency loss and tends to involve the lower frequencies with increasing age. Support for these observations can be derived from other reported data (6, 8). The present data on patients with low-tone SNHL, however, did not show the same tendency, because these patients were free from significant SNHL at the higher frequencies.

Most of our patients showed normal BAEP findings; the (few) abnormal findings can be attributed to false positivity. Others also reported normal BAEP findings in FSHD (12, 14, 18). The finding of a decreased I-V interval in 2 patients with severe hearing loss (10) would suggest misinterpretation of the wave forms.

Voit et al. (10) reported normal bithermal caloric responses in all 10 of their FSHD patients. VH was a significant finding in the present study, i.e. it occurred more often than could be explained by false positivity alone. This finding was significantly associated with women in the 5th generation of 2 families. We have also reported the finding of VH in a recent study on myotonic dystrophy (19). One possible explanation is that an enhanced VOR gain develops secondary to diminished head movements as a result of useful plastic adaptation of spatial orientation and gaze stabilization behaviour.

The oculomotor system appeared to be spared in the present cases of FSHD.

Although genetic studies have indicated genetic homogeneity, the variety of features detected in the present study clearly demonstrates clinical heterogeneity, which may relate to variability in expression or nonpenetrance. Not only hearing loss, but also retinal vasculopathy, which was found in 50% of the patients (25), appeared to show great variability within the present and other (genetically homogeneous) FSHD families, independent of the severity of the myopathy. This has been attributed to pleiotropic effects of the FSHD gene (25).

ACKNOWLEDGEMENTS

We thank Henriette Koch, Lucas Mens, John Noten and Martien Nicolassen for their assistance and the patients for their cooperation.

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